38. (Thrice Amended) An isolated [gene] polynucleotide which codes for a [BS200] protein having the amino acid sequence with at least [50%] 90% identity with SEQUENCE ID NO 31.

39. (Thrice Amended) An isolated [gene] polynucleotide comprising DNA having at least [50%] 90% identity with SEQUENCE ID NO 15 and SEQUENCE ID NO 16, or complements thereof.

REMARKS

The disclosure is objected to by the Examiner because of the following informalities:

(a) Figures 3A and 3B described at page 11 are not in the application and it is not clear that they have been filed; and

(b) The use of "SEQUENCE ID NO" as a sequence designator in the specification and claims instead of "SEQ ID NO."

Applicant requests that this objection be held in abeyance until subject matter is deemed allowable.

Claims 11-14, 38, 39 and 45-49 are rejected under 35 U.S.C. 101 because the claimed nucleic acids are not supported by either a specific and substantial asserted utility or a well established utility.

Applicant vigorously disagrees. BS200 is a previously unknown polynucleotide that codes for a protein 516 amino acid long and is useful as a diagnostic marker for diseases of the breast due to its abundance in breast tissue.

Based on quantitative analysis of the occurrence of the BS200 polynucleotide in human breast tissue samples compared to human tissue samples representing the body as a whole, BS200 is approximately 7 times more abundant in breast tissue than in the rest of the body. {Data are obtained from the Lifeseq database developed by Incyte Pharmaceuticals.} As is known scientists skilled in the cancer diagnostic arts, a gene product, such as a protein or messenger RNA (mRNA) coding for the protein, which is more prevalent and highly specific to one tissue type than other tissue types, is extremely useful as a marker for the detection of disease in that tissue. If a protein appears in a

tissue or body compartment where its normal occurrence is very low or non-existent, then the specific tissue in which the protein is normally found is in a diseased state. This is because the disease causes an alteration to the protein-specific tissue resulting in the protein escaping from its normal tissue into another. There are three main conditions which cause a tissue-specific protein to exist outside its specific host tissue: massive trauma, ischemia and hypertrophic proliferation. Thus, if a patient has not experienced a massive trauma or ischemia, detection of a tissue-specific protein outside that protein's host tissue indicates that the precise disease is hypertrophic proliferation of that tissue, the most serious form being cancer. There are many examples of the diagnostic use of tissue-specific protein markers. For instance, the appearance of prostate specific antigen (PSA) in seminal plasma is normal, but its detection in blood is indicative of prostate cancer. Further, the appearance of PSA messenger RNA (mRNA) in blood is indicative of prostate cancer. Likewise, the appearance of carcinoembryonic antigen (CEA) in colon and stool is normal, but its detection in blood at elevated levels is indicative of colorectal cancer. The attached Exhibit A illustrates the usefulness of tissue specific molecules which, upon detection in circulation, indicate proliferative disease. For Example, Exhibit A states that CEA is expressed in normal adult tissue but is detected in serum in patients with colorectal and other carcinomas. (p. 67, col. 2). This journal article explains how a tissue specific molecule, expressed in the colon in normal individuals, is drained into lymph and blood vessels upon colon tumor growth. (Fig. 5) Thus, the above scientific facts support the utility of BS200 and illustrate that the appearance of BS200 protein or mRNA in a patient blood sample is indicative of breast disease in that patient.

In addition to high tissue specificity, BS 200 has significant epidermal growth factor (EGF)-like domains. It is well known to those skilled in the art that cancer is a disease whereby growth control mechanisms are no longer functional. These growth control mechanisms involve interactions between proteins facilitated by specific domains, especially EGF domains. Hence, the EGF domain on BS200 directly links it to growth control mechanisms which are integral to cancer onset and progression.

BS 200 clearly has EGF-like domains recognizable to one in the art. Specifically, EGF-like domains are sequences of about forty amino acid residues in the sequence of EGF. These domains have been shown to be present in a large number of membrane-bound and extracellular proteins, including BS 200. The EGF domain includes six

cysteine residues which have been shown to be involved in disulfide bonds (C1-C3, C2-C4, C5-C6). There are 3 signature sequences for EGF:

1. EGF-like domain signature which uses the C terminal sequence of the EGF domain as a consensus sequence;
2. Calcium binding EGF-like domain signature which uses the N terminal sequence of the EGF domain as a consensus sequence; and
3. Laminin-type EGF-like domain signature.

There are 6 Calcium-binding EGF-like domain structures (residues 45-84, 86-111, 128-167, 323-362, 364-401, and 403-442) in BS 200. These are the full length EGF-like sequences which were identified with the EGF-like domain signature as well as the calcium binding EGF-like domain signature. There are also 2 other EGF-like domains (residues 177-213 and 286-321)in BS200 that were identified solely by the EGF-like domain signature.

The Calcium-binding EGF-like domain structures found in BS 200 are important because proteins that are known to contain calcium-binding EGF-like domains include CASPases (which degrade the extracellular matrix proteins and have been shown to be involved in metastasis), and transforming growth factor beta-1 binding protein, thrombospondins 1 and 2 (which mediate cell-to-cell and cell-to-matrix interactions).

Further, proteins currently known to contain one or more copies of an EGF-like pattern include CASPases, transforming growth factor beta-1 binding protein, thrombospondins 1 and 2, transforming growth factor alpha, selectins including lymph-node homing receptor (L-selectin), tyrosine-protein kinase receptors Tek and Tie (shown to be involved in cancer), and urokinase (shown to be involved in metastasis).

EGF domains are also involved in binding to the ErbB family of receptors, long associated with cancer, as shown by Exhibit B. This abstract clearly demonstrates the link between EGF domains and growth mechanisms or factors.

Thus, it is evident that the EGF- domains on BS 200 link this molecule to metastatic disease.

The Examiner is reminded of the proper standard under the Revised Interim Utility Guidelines which specifically states that utility is acceptable if it is "believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning

provided". The Guidelines continue stating "[A]n assertion is credible unless (a) the logic underlying the assertion is **seriously** flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion", (emphasis added). Simply put, the threshold to be met by Applicant is a **credible assertion** of utility, not the extraordinarily high threshold improperly held by the Examiner. Clearly, the appearance of a secreted BS200 gene product outside the breast tissue itself, such as in whole blood, urine, stool or serum, indicates a form of breast disease, akin to the presence of common markers such as PSA and CEA found in blood outside of their prevalent tissue type. BS200's use in diagnostic test in order to determine whether a patient has a disease of the breast unquestionably illustrates a credible utility.

Therefore, it is requested that this rejection be withdrawn.

Claims 11-14, 38, 39 and 45-49 are also rejected under 35 U.S.C. 112, first paragraph, as being nonenabled. Specifically, the Examiner states that since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above in paragraph 3, one skilled in the art clearly would not know how to use the claimed invention.

Based on the above arguments, it is respectfully requested that this rejection be withdrawn.

Claims 11-14, 38, 39 and 45-49 are rejected under 35 U.S.C. 112, first paragraph. The Examiner states the specification discloses the claimed nucleotide sequences, SEQ ID NOS: 1-3, 6, 9 and 14-16 as well as the amino acid sequence, SEQ ID NO: 31, however, a representative number of polynucleotides comprising sequences having "at least 50% identity" with sequences recited in the claims are not described therein. Further, polynucleotides comprising "a polynucleotide sequence of at least about 10 or 12 or 15 or 20 nucleotides are not described in the specification.

Thus, applicant has raised the percent identity and deleted fragment type language and it is respectfully requested that this rejection be withdrawn.

Claims 11-14, 38, 39 and 45-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOS: 1-3, 6, 9, 14-16 and 31, does not reasonably provide enablement for polynucleotides comprising sequences

having "at least 50% identity" to these sequences or their complements or an "isolated gene" or polynucleotides of "at least" 10 or 12 or 15 or 20 nucleotides.

Based on the above comments and amendments to the claims, it is respectfully requested that this rejection be withdrawn.

Claims 11-14, 38, 39 and 45-48 are rejected under 35 U.S.C. 112, second paragraph. Specifically, claims 11 and 45-48 are confusing and lack antecedent basis in the redundant use of "polynucleotide" and it is suggested to change the third "polynucleotide" in claim 11 to --nucleotide sequence--. Further claim 38 lacks proper antecedent basis for "the amino acid sequence" and it is suggested to change "the" to --an--. Lastly, claim 39 is confusing because it is unclear how SEQ ID NO: (sic SEQUENCE ID NO) 15 and 16 are to be combined or if they are to be combined for determining the "DNA having at least 50% identity" therewith and it is suggested to change "and" to --or-- or to clarify otherwise.

Applicant has complied with the Examiner's suggestion and it respectfully requested that this rejection be withdrawn.

Claims 11 and 45-48 are rejected under 35 U.S.C 102(a or b) as anticipated by Hillier et al. for SEQ ID NO:3 and Matsubara et al. for SEQ ID NOS: 9, 15 and 16 because each of the references discloses polynucleotide sequence that "has at least 50% identity" with a polynucleotide of claim 11 and for claims 45-48, each of the reference sequences comprises "at least about" 10 or 12 or 15 or 20 nucleotides.

Therefore, applicant has raised the percent identity and omitted fragment type language. It is requested that this rejection be withdrawn.

Claims 12-14 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hillier et al. and Matsubara et al.

Based on the above amendments which obviate this rejection, it is respectfully requested that this rejection be withdrawn.

Claim 39 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Matsubara et al. (AC T25603 (Geneseq) WO 95/14772). The Examiner states that this reference meets the limitation of

"comprising DNA that has at least 50% identity with [SEQ ID NO:15, SEQ ID NO:16] or complements thereof" wherein the recited "isolated gene" has no defining characteristics of a gene such as encoding an amino acid sequence.

Based on the amendments to the claims, it is respectfully requested that this rejection be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, the aforementioned application is in condition for allowance and Applicant requests that the Examiner withdraw all outstanding objections and rejections and to pass this application to allowance.

Respectfully submitted,

P. A. Billing-Medel, *et al.*

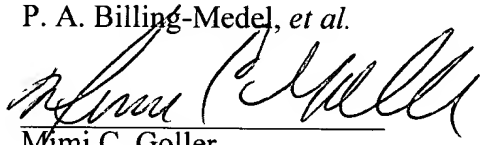

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EXHIBIT B

From 'Vitamins and Hormones' 2000, Vol 59, pp99-131

The EGF Domain: requirements for binding to receptors of the ErbB family.

EGF has been the prototype growth-stimulating peptide for many years. It has a characteristic structure with three disulfide bridges, which is essential for its activity. However, many other proteins, including both growth factors and proteins with unrelated functions, have similar EGF-like domains. This indicates that besides a characteristic conformation provided by the EGF-like domain, specific amino acids are required to provide specificity in protein functioning. Currently, more than 10 different growth factors with an EGF-like domain have been characterized which all exert their action by binding to the four members of the ErbB family of receptors. In this review, studies are described on the structure-function relationship of these EGF-like growth factor molecules in an attempt to analyze the individual amino acids that determine their binding specificity to the individual members of the ErbB family.